KENTUCKY PANDEMIC INFLUENZA PREPARDNESS PLAN
ANTIVIRAL DISTRIBUTION AND USE SUPPLEMENT VI

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SUMMARY OF PUBLIC HEALTH ROLES AND RESPONSIBILITIES FOR ANTIVIRAL DISTRIBUTION AND USE

Interpandemic and Pandemic Alert Periods

Department for Public Health/Local Health Departments

- Use antivirals in medical management of cases of novel strains of influenza
- Procure and maintain local stockpiles of antiviral drugs if/when funding permits
- Develop state-based plans for distribution and use of antiviral drugs during a pandemic

Pandemic Period

Department for Public Health/Local Health Departments

- Prepare to activate state-based plans for distributing and administering antivirals to persons in priority groups.
- Review modifications, if any, to interim recommendations on antiviral prophylaxis in selected groups or circumstances.
- Accelerate training on appropriate use of antiviral drugs among public health staff and healthcare partners.
- Work with other governmental agencies and non-governmental organizations to ensure effective public health communications.

If pandemic influenza is detected in the United States, state and local health departments will work with healthcare partners to:

- Distribute and deliver stockpiled supplies of antivirals, as appropriate, to healthcare facilities that will administer them to priority groups.
- Work with HHS to monitor antiviral drug use and effectiveness.
- Work with HHS to monitor and investigate adverse events.
- Provide updated information to the public via the news media.

I. RATIONALE

Drugs with activity against seasonal influenza viruses ("antivirals") in 2005-2006 and 2006-2007 include the neuraminidase inhibitors (*oseltamivir* and *zanamivir*). The adamantanes (*amantadine* and *rimantadine*) were ineffective against recent seasonal influenza viruses. Appropriate use of these agents during an influenza pandemic may reduce morbidity and mortality and diminish the overwhelming demands that will be placed on the healthcare system. Antivirals might also be used during the Pandemic Alert Period in limited attempts to contain small disease clusters and potentially slow the spread of novel influenza viruses. A huge and uncoordinated demand for antivirals early in a pandemic could rapidly deplete national and local supplies. Preparedness planning for optimal use of antiviral stocks is therefore essential.

II. OVERVIEW

The Antiviral Supplement provides recommendations to state and local partners on the distribution and use of antiviral drugs for treatment and prophylaxis during and influenza pandemic. Stockpiled antivirals will be supplied from the federal level. State and local stockpiles will depend upon funding and availability. The Interpandemic and Pandemic Alert Period recommendations focus on preparedness planning for the rapid distribution and use of antiviral drugs (e.g., distribution to priority groups, legal preparedness, training, and data collection on use, effectiveness, safety, and the development of drug resistance). These recommendations also cover the use of antiviral drugs in the management and containment of cases and clusters of infection with novel strains of influenza, including influenza A (H5N1) and other strains with pandemic potential.

The Pandemic Period recommendations focus on the local use of antiviral drugs in three situations:

1. When pandemic influenza is sporadically reported in the United States (without evidence of spread in the United States)
2. When there is limited transmission of pandemic influenza in the United States
3. When there is widespread transmission in the United States. National recommendations for optimal use of limited stocks of antivirals will be updated throughout the course of an influenza pandemic to reflect new epidemiologic and laboratory data. Interim recommendations will also be updated as an effective influenza vaccine becomes available.

Additional issues that may be of interest to healthcare partners who administer antiviral drugs are outlined in the Healthcare Planning Supplement.

III. GUIDELINES FOR THE INTERPANDEMIC AND PANDEMIC ALERT PERIODS

A. Use of Antivirals in Management of Cases of Novel Influenza

Influenza infections may be due to:

1. Interpandemic (i.e., 'normal') seasonal strains of influenza A
2. Novel strains of influenza that do not appear to be easily transmissible but could be precursors to human pandemic strains (e.g., influenza A [H5N1] viruses)
3. Novel strains of influenza that demonstrate person-to-person transmission and therefore have pandemic potential (e.g., a new human pandemic strain)

In this supplement, the term "novel strains of influenza" is used to refer to avian or animal influenza strains that can infect humans (like avian influenza A [H5N1]) and new or re-emergent human influenza viruses that cause cases or clusters of human disease. Criteria for early detection and identification of novel strains of influenza are discussed in the Clinical Guidelines Supplement.

B. Use of Antivirals for Treatment

A patient with a suspected case of avian influenza A (H5N1) or another novel strain of influenza should be isolated as described in the Transmission of Disease Supplement and treated in accordance with the clinical algorithm for the Pandemic Alert Period provided in the Healthcare Planning Supplement. As of fall 2005, the recommendation for treatment includes the use of oseltamivir or zanamivir, administered as early as possible and ideally within 48 hours after onset of symptoms. These neuraminidase inhibitors are preferred because the majority of avian influenza A (H5N1) viruses currently affecting humans are resistant to amantadine and rimantadine, and resistance to these drugs typically develops rapidly when they are used for treatment of influenza. Although resistance to zanamivir and oseltamivir can be induced in influenza A and B viruses *in vitro*, multiple passages in cell culture are usually required to produce neuraminidase inhibitor resistance, in contrast with adamantane resistance, which can develop after a single passage. Because the neuraminidase inhibitors have different binding sites for the enzyme, cross-resistance between zanamivir- and oseltamivir-resistant viruses is variable.

C. Use of Antivirals for Prophylaxis of Contacts

State and local health departments, in consultation with CDC, will consider whether it is necessary and feasible to trace a patient's close contacts and provide them with postexposure antiviral prophylaxis**.** Close contacts may include family, schoolmates, workmates, healthcare providers, and fellow passengers if the patient has been traveling. If deemed necessary by public health authorities, these persons may receive post-exposure prophylaxis with oseltamivir, as zanamivir is not currently indicated for prophylaxis. Zanamivir is now recommended for chemoprophylaxis.

If the exposure to the novel influenza virus strain occurs during the regular influenza season, the patient's healthcare contacts (who may also care for persons with seasonal influenza) should be vaccinated against seasonal influenza to reduce the possible risk of co-infection and reassortment of seasonal and novel strains.

D. Use of Antivirals for Containment of Disease Clusters

In special circumstances, state and local health departments could consider "targeted antiviral prophylaxis" as a community-based measure for containing small clusters of infection with novel strains of influenza. This measure could be implemented in small, well-defined settings such as the initial introduction of a virus with pandemic potential into a small community or a military base. However, once a pandemic is underway, such a strategy would not represent an efficient use of limited antiviral supplies.

Because targeted antiviral prophylaxis would require rapid delivery and administration of substantial stocks of antiviral drugs, its feasibility should be evaluated in light of antiviral drug supply and interim recommendations on antiviral drug use during a pandemic. Targeted antiviral prophylaxis would involve investigation of disease clusters, administration of antiviral treatment to persons with confirmed or suspected cases of pandemic influenza, and provision of drug prophylaxis to all persons in the affected community. Targeted antiviral prophylaxis would also require intensive case-finding in the affected area as well as effective communication with the affected community.

IV. PREPAREDNESS PLANNING FOR USE OF ANTIVIRALS DURING PANDEMIC

A. National Recommendations on Use of Antivirals During a Pandemic

The Department for Health and Human Services (HHS) is working with private-sector partners to increase production of antivirals and to procure additional stocks of antivirals for the Strategic National Stockpile (SNS) (http://www.HHS.gov/nvpo/pandemicplan/). Despite these efforts, demand for antivirals during an influenza pandemic is likely to far outstrip supplies available in stockpiles or through usual channels of distribution.

- A list of priority groups for receiving antiviral treatment or prophylaxis and the rationale for prioritization are provided in the NVAC/ACIP Recommendations Appendix. During an actual pandemic, these recommendations could be modified, based on the characteristics of the causative virus (e.g., drug susceptibilities, initial geographic distribution, fatality rate, age-specific morbidity and mortality rates) and the effectiveness of implemented strategies.

B. State-Level Planning

- State-based planning for antiviral includes:

- Obtaining antiviral drugs from national, state, and local stockpiles if available, and their distribution to priority groups by healthcare providers
- Data collection on drug use,
- Drug-related adverse events
- Drug resistance.

C. Procurement

Examples of planning steps for state-level procurement of antivirals include:

- Estimating the quantities of antiviral drugs that will be needed for treatment and prophylaxis of priority groups (see below)
- Identifying sources of antiviral drugs (e.g., federal supplies from the SNS and if available state stockpiles and private sector).

The establishment of state, local, or institutional stockpiles should take into account the expiration dates of the purchased material. All drugs are marked with an expiration date, based on review of stability data, at the time of manufacture. However, when purchased, the drugs might have been stored for some time in warehouses so that the time to expiration might be shorter than the time from initial manufacture to expiration date. Moreover, one shipment might consist of several batches with different expiration dates. Antivirals maintained in the national stockpile may be tested for potency and dating extended under the U.S. Food and Drug Administration's (FDA) shelf life extension program. Currently, state stockpiles are not included in this program.

D. Establishing Priority Groups

Based on interim recommendations on priority groups for antiviral treatment and prophylaxis (NVAC/ACIP Recommendations), state and local health authorities should determine how certain priority groups (e.g., public safety workers, essential service providers, and key decision makers) will be defined in their jurisdictions. These recommendations and enumerations can be found in the Recommendations on Antiviral Use portion of the state pandemic plan.

E. Distributing and Dispensing Antivirals to Priority Groups

Planning steps for distribution of antivirals to priority groups might include:

- Estimating the size and needs of priority groups in local jurisdictions, using interim recommendations
- Assessing antiviral stocks available at the state, local, and hospital levels if available
- Establishing a mechanism to request antivirals from the federal stockpile, if needed (see below)
- Activating pre-existing plans for the transport, receipt, storage, security, tracking, and delivery of:

  - Antiviral stocks for use in treatment to hospitals, clinics, nursing homes, alternative care facilities, and other healthcare institutions. Prompt dispensing to point-of-care locations is crucial, because clinical efficacy for these agents has been demonstrated when treatment begins within 48 hours of the onset of symptoms.
  - Antiviral stocks for use in post-exposure prophylaxis (e.g., for direct contacts of infected patients)
  - Antiviral stocks for use in prophylaxis (e.g., if recommended for healthcare workers, public safety workers, and essential service providers)
- Considering the use of standing orders for treatment of certain priority groups, such as hospitalized patients and healthcare workers
- Developing a communication plan to explain the rationale for establishing these target groups

The decision to deploy federal assets from the SNS during an influenza pandemic will be made by HHS officials, as it would be during any public health emergency. Each state and federal agency with direct patient care responsibilities should designate a representative (e.g., the state epidemiologist or public health director) to make emergency requests for federal assets in the SNS.

Federal supplies of antivirals will be delivered to a site designated by state planners in each state or large city (e.g., state health department; existing SNS receipt, storage, staging site). State SNS coordinators should provide logistical guidance on the receipt and distribution of federal assets to priority groups.

Kentucky's SNS plan can be found in Kentucky Emergency Operations Plan Appendix M-10 (Strategic National Stockpile Program).

F. Monitoring and Data Collection

To ensure optimal use of antiviral drugs during an influenza pandemic, state and local health departments and healthcare partners should work with federal officials and collect data on:

- Distribution of state or federal supplies of antiviral drugs
- Occurrence of adverse events following administration of antiviral drugs

State and local departments could also participate in federal efforts to collect data on:

- Effectiveness of treatment and prophylaxis
- Development of drug resistance

(1) Distribution. Allocation and distribution of antiviral drugs from state and local health departments to drug delivery or dispensing sites will be established based on state and local pandemic plans. Health departments should develop strategies to

monitor drug distribution and use, assessing whether drugs are being effectively targeted to priority groups and whether distribution is equitable within those groups (e.g., among racial and ethnic minorities and persons of different socioeconomic levels).

(2) Antiviral effectiveness. Studies to evaluate the effectiveness of antiviral drug use during a pandemic will be conducted by federal agencies in collaboration with state and local health departments and other healthcare and academic partners. The effectiveness of antiviral therapy and prophylaxis will be assessed by comparing rates of severe influenza-related illness and death among treated and untreated persons and among persons who did and did not receive prophylaxis. Analyses of antiviral drug effectiveness should take into account characteristics that will vary among individuals and those that may vary over time, such as diagnostic practices, length of time to initiate therapy, and changes in the pandemic virus.

(3) Adverse events. Serious adverse events associated with the use of antiviral drugs for prophylaxis and treatment of influenza should be reported to the FDA, using the MedWatch monitoring program. During an influenza pandemic, state and local health departments can assist in this effort by providing protocols and information to healthcare providers and encouraging hospitals to download MedWatch forms (available at http://www.fda.gov/medwatch/) for distribution to patients. Adverse events reported to MedWatch are collated and analyzed by the FDA's Adverse Events Reporting System (AERS).

Use of antivirals will be much greater during a pandemic than during a regular influenza season. To help improve the detection of serious adverse effects (especially rare effects or effects in vulnerable populations), additional efforts to encourage recognition and reporting of adverse events will be needed. These efforts might include:

- Active monitoring for adverse events observed at emergency rooms, through the National Electronic Injury Surveillance System Cooperative Adverse Drug Event project (NEISS-CADE)
- Local campaigns to educate healthcare workers about the recognition and reporting of adverse events
- Distribution of MedWatch forms and descriptions of known adverse events to each end-user who receives antiviral drugs

In addition, the CDC, FDA, and AHRQ will explore the use of existing drug-monitoring systems that have access to individual health utilization records that may

allow active, population-based surveillance for adverse events following the use of antivirals for treatment or prophylaxis.

(4) Antiviral drug resistance. CDC will work with state and local partners to monitor the development of resistance to antivirals. Because resistance to M2 inhibitors may involve a single base pair change, resistance may develop rapidly if these drugs are used widely. Information about resistance to M2 inhibitors (i.e. the adamantanes and neuraminidase inhibitors can be found in the July 2005 recommendations of the ACIP (http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf) .

Global surveillance for neuraminidase resistance during a pandemic will also be conducted by the Neuraminidase Inhibitor Susceptibility Network (NISN). The global NISN was established in 1999 to address public health and regulatory concerns regarding the potential emergence and consequences of drug resistance in influenza viruses following the introduction of the influenza neuraminidase inhibitor (NI) class of antiviral agents. The Network includes representatives of each of the four World Health Organization (WHO) global influenza reference laboratories and scientists from regions of the world where increasing use of these drugs is anticipated.

CDC will test the drug susceptibilities of viruses isolated from different age groups and geographic groups over the course of the pandemic (see Antiviral Effectiveness above). State and local health departments should encourage clinicians to obtain specimens from patients who develop severe disease while receiving treatment or prophylaxis. State health departments should provide these specimens on a periodic basis, preferably after testing them by RT-PCR, viral culture, or rapid diagnostic testing to confirm the presence of novel strains of influenza A.

Surveillance for antiviral resistance may be particularly important during the later stages of the pandemic, especially if M2 inhibitor agents (i.e. adamantanes) have been widely used. Under these circumstances, the detection of widespread M2 inhibitor resistance might require a re-evaluation of priorities for prophylaxis and treatment.

G. Contingency Planning for Investigational New Drug (IND) Use

State and local health departments should be prepared to distribute unlicensed antiviral drugs (if needed) under FDA's Investigational New Drug (IND) provisions. IND provisions require strict inventory control and recordkeeping, completion of a signed consent form from each person who receives the medication, and mandatory reporting of specified types of adverse events. IND provisions also require approval of the protocol and consent form by an Institutional Review Board (IRB). The FDA regulations permit the use of a national or "central" IRB. A treatment IND is one IND mechanism that FDA has available for use and is especially suited for large scale use of investigational products (http://www.access.gpo.gov/nara/cfr/waisidx_99/21cfr_99.html).

As an alternative to IND use of an unapproved antiviral drug, HHS may utilize the drug product under Emergency Use Authorization procedures as described in the FDA draft *Guidance Emergency Use Authorization of Medical Products* http://www.fda.gov/cber/gdlns/emeruse.pdf

V. RECOMMENDATIONS FOR THE PANDEMIC PERIOD

Interim recommendations for use of antivirals may be updated throughout the course of an influenza pandemic to reflect current epidemiologic and laboratory data. Interim recommendations may also be updated as an effective influenza vaccine becomes available.

A. When pandemic influenza is reported abroad, or sporadic pandemic influenza cases are reported in the United States, without evidence of spread

If an influenza pandemic has begun in other countries, state and local health departments should:

- Use antiviral drugs in the management of persons infected with novel strains of influenza and their contacts.
- Work with healthcare partners to consider providing antiviral prophylaxis to persons at highest risk for pandemic influenza. Examples of such persons include:
  - Public health workers who investigate suspected cases of pandemic influenza
- Meet with local partners and stakeholders to review the state-based antiviral drug distribution plan. As part of this effort, state and local partners could:
  - Modify the distribution plan to take into account possible updated recommendations on target groups and updated information on projected supplies of antiviral drugs.
  - Notify the medical community about the status of the plan and the availability of antiviral drugs.
  - Disseminate public health guidelines that encourage drug-use practices that help minimize the development of drug resistance.
  - Provide the public with information on interim recommendations and their rationale for the use of antiviral drugs during an influenza pandemic.
- Work with federal partners to monitor the safety and effectiveness of drugs and ensure that available antivirals are used in accordance with federal and local recommendations.

B. When there is limited transmission of pandemic influenza in the United States

When there is limited transmission of pandemic influenza in the United States, state and local health departments should:

- Activate state-based plans for targeting antiviral drugs to priority groups for prophylaxis and treatment.

- Request antiviral drugs, as needed, from previously identified sources, including the SNS.
- Continue to work with healthcare partners to ensure appropriate use of antivirals in the medical management of early cases and contacts.
- Work with federal partners to begin monitoring the safety and effectiveness of drugs and ensure that available antivirals are used in accordance with federal and local recommendations.

C. When there is widespread transmission of pandemic influenza in the United States

When transmission of pandemic influenza has become widespread, the paramount goals of antiviral use will be to treat those at highest risk of severe illness and death, and to preserve the delivery of healthcare and other essential critical services through early treatment and limited prophylaxis.

After a vaccine becomes available, antiviral drugs may be used to protect persons who have an inadequate vaccine response (e.g., the elderly and those with underlying immunosuppressive disease) as well as persons with contraindications to vaccination, such as anaphylactic hypersensitivity to eggs or other vaccine components.

Until the pandemic has waned, state and local health departments should continue to work with healthcare and federal partners to monitor the safety and effectiveness of antivirals and to encourage appropriate drug use practices that help minimize the development of drug resistance.

APPENDIX A
Recommendations on Pandemic Antiviral Use

The following recommendations are reflective of the National Vaccine Advisory Committee (NVAC) recommendations issued on July 19, 2005. NVAC recognizes that recommendations for antiviral drug use will need to be reconsidered at the time of a pandemic when information of the available drug supply, epidemiology of disease, and impacts on society are known. Kentucky will comply with recommendations set forth by NVAC, the Department for Health and Human Services (HHS), and the Centers for Disease Control and Prevention (CDC) and will implement any changes made by these agencies to the recommendations on pandemic antiviral use. The committee considered the primary goals of a pandemic response to decrease health impacts including severe morbidity and death. Minimizing societal and economic impacts were considered secondary and tertiary goals.

A. Critical Assumptions

Assumptions regarding groups at highest risk during a pandemic and impacts on the healthcare system and other critical infrastructures are the same as those underlying the vaccine priority recommendations. Additional assumptions specific for antiviral drugs included:

- Treatment with a neuraminidase inhibitor (oseltamivir [Tamiflu®] or zanamivir [Relenza®]) will be effective in decreasing risk of pneumonia, will decrease hospitalization by about half (as shown for interpandemic influenza), and will also decrease mortality.
- Antiviral resistance to the adamantanes (amantadine and rimantadine) may limit their use during a pandemic.
- The primary source of antiviral drugs for a pandemic response will be the supply of antiviral drugs that have been stockpiled. Before annual influenza seasons about 2 million treatment courses of oseltamivir are available in the U.S. U.S.-based production of oseltamivir is being established; expected capacity is projected at about 1.25 million courses per month.
- Treating earlier after the onset of disease is most effective in decreasing the risk of complications and shortening illness duration. Generally, treatment should be given within the first 48 hours.
- Assumptions for the amount of antiviral drug needed for defined priority groups is based on the population in those groups and assumptions that 35% of persons in the priority groups will have influenza-like illness and 75% will present within the first 48 hours and be eligible for treatment. For persons admitted to the hospital, the committee assumed that 80% would be treated, as the 48-hour limit may sometimes be relaxed in more ill patients.
- Unlike vaccines, where each tier would be protected in turn as more vaccine is produced, for antiviral drugs, the number of priority groups that can be covered would be known at the start of the pandemic based on the amount of drug that is

stockpiled. Additional supply that would become available during the pandemic could provide some flexibility.

Table D-2: Antiviral Drug Priority Group Recommendations*

	Group	Estimated population (millions)	Strategy**	# Courses (millions)		Rationale
				For target group	Cumulative	
1	Patients admitted to hospital***	10.0	T	7.5	7.5	Consistent with medical practice and ethics to treat those with serious illness and who are most likely to die.
2	Health care workers (HCW) with direct patient contact and emergency medical service (EMS) providers	9.2	T	2.4	9.9	Healthcare workers are required for quality medical care. There is little surge capacity among healthcare sector personnel to meet increased demand.
3	Highest risk outpatients—immunocompromised persons and pregnant women	2.5	T	0.7	10.6	Groups at greatest risk of hospitalization and death; immunocompromised cannot be protected by vaccination.
4	Pandemic health responders (public health, vaccinators, vaccine and antiviral manufacturers), public safety (police, fire, corrections), and government decision-makers	3.3	T	0.9	11.5	Groups are critical for an effective public health response to a pandemic.
5	Increased risk outpatients—young children 12-23 months old, persons	85.5	T	22.4	33.9	Groups are at high risk for hospitalization and death.

	Group	Estimated population (millions)	Strategy**	# Courses (millions)		Rationale
				For target group	Cumulative	
	>65 yrs old, and persons with underlying medical conditions					
6	Outbreak response in nursing homes and other residential settings	NA	PEP	2.0	35.9	Treatment of patients and prophylaxis of contacts is effective in stopping outbreaks; vaccination priorities do not include nursing home residents.
7	HCWs in emergency departments, intensive care units, dialysis centers, and EMS providers	1.2	P	4.8	40.7	These groups are most critical to an effective healthcare response and have limited surge capacity. Prophylaxis will best prevent absenteeism.
8	Pandemic societal responders (e.g., critical infrastructure groups as defined in the vaccine priorities) and HCW without direct patient contact	10.2	T	2.7	43.4	Infrastructure groups that have impact on maintaining health, implementing a pandemic response, and maintaining societal functions.
9	Other outpatients	180	T	47.3	90.7	Includes others who develop influenza and do not fall within the above groups.
10	Highest risk outpatients	2.5	P	10.0	100.7	Prevents illness in the highest risk groups for hospitalization and death.

	Group	Estimated population (millions)	Strategy**	# Courses (millions)		Rationale
				For target group	Cumulative	
11	Other HCWs with direct patient contact	8.0	P	32.0	132.7	Prevention would best reduce absenteeism and preserve optimal function.

*The committee focused its deliberations on the domestic U.S. civilian population. NVAC recognizes that Department of Defense (DoD) needs should be highly prioritized. A separate DoD antiviral stockpile has been established to meet those needs. Other groups also were not explicitly considered in deliberations on prioritization. These include American citizens living overseas, non-citizens in the U.S., and other groups providing national security services such as the border patrol and customs service.

**Strategy: Treatment (T) with oseltamivir [Tamiflu®] requires a total of 10 capsules and is defined as 1 course. Post-exposure prophylaxis (PEP) also requires a single course. Prophylaxis (P) with oseltamivir [Tamiflu®] is assumed to require 40 capsules (4 courses) though more may be needed if community outbreaks last for a longer period.

***There are no data on the effectiveness of treatment at hospitalization. If stockpiled antiviral drug supplies are very limited, the priority of this group could be reconsidered based on the epidemiology of the pandemic and any additional data on effectiveness in this population.

B. Definitions and rationale for draft priority groups

1. Persons admitted to hospital with influenza infection

a) Definition

Persons admitted to acute care facilities (traditional or non-traditional with a clinical diagnosis of influenza; laboratory confirmation not required). Excludes persons admitted for a condition consistent with a bacterial superinfection (e.g., lobar pneumonia developing late after illness onset) or after viral replication and shedding has ceased (e.g., as documented by a negative sensitive antigen detection test)

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

This group is at greatest risk for severe morbidity and mortality. Although there are no data to document the impacts of antiviral drug treatment among persons who already suffer more severe influenza illness, benefit is biologically plausible in persons with evidence of ongoing virally mediated pathology (e.g., diffuse pneumonia, ARDS). Providing treatment to those who are most ill is also consistent

with standard medical practices, would be feasible to implement, and would be acceptable to the public.

d) Population size

The number of persons admitted to hospital in an influenza pandemic would vary substantially depending on the severity of the pandemic and on the ability to expand inpatient capacity, if needed.

e) Unresolved issues

More specific guidance should be provided to healthcare workers on implementing antiviral treatment, including when and when not to treat. In some persons with severe illness, the ability to take oral medication or its absorption may be important issues. For infants <1 year old admitted to hospital, decisions about whether to treat with antiviral drugs may depend on the child's age and potential risk versus benefit as the neuraminidase inhibitors are not licensed for use in infants. If possible, data on time from symptom onset to hospital admission, current use of antiviral drug treatment among inpatients, and its impacts should be collected during interpandemic influenza seasons.

2. Healthcare workers and emergency medical service providers who have direct patient contact

a) Definition

Persons providing direct medical services in inpatient and outpatient care settings. Includes doctors, nurses, technicians, therapists, EMS providers, laboratory workers, other care providers who come within 3 feet of patients with influenza, and persons performing technical support functions essential to quality medical care.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Maintaining high quality patient care is critical to reduce health impacts of pandemic disease and to prevent adverse outcomes from other health conditions that will present for care during the pandemic period. Treatment of healthcare providers will decrease absenteeism due to influenza illness and may decrease absenteeism from fear of becoming ill, given the knowledge that treatment can prevent serious complications of influenza. Good data exist documenting the impacts of early treatment on duration of illness and time off work, and on the occurrence of complications such as lower respiratory infections. Treating healthcare providers is feasible to implement, especially for inpatient care providers who can be provided drugs through the occupational health clinic. It also would be acceptable to the public, who would recognize the importance of maintaining quality healthcare and would understand that persons with direct patient contact are putting themselves at increased risk.

d) Population size

There are about 12.6 million persons designated as healthcare workers by the Bureau of Labor Statistics and about 820,000 EMS providers. Among HCWs, two-thirds are estimated to provide direct patient care services.

e) Unresolved issues

Further work is needed to hone definitions and estimate population sizes.

Implementation issues include the approach to identifying healthcare providers who would be eligible for treatment and where the treatment would be provided, particularly for outpatient care providers.

3. Outpatients at highest risk for severe morbidity or mortality from influenza infection

a) Definition

The ACIP defines groups at high risk (or increased risk) of complications from influenza infection during annual outbreaks based on age (6-23 months and >65 years) and underlying illnesses. Among this population of about 88 million persons, some can be identified who are at highest risk of severe disease and death. These include persons with hematopoietic stem cell transplants (HSCT) and solid organ transplants; those with severe immunosuppression due to cancer therapy or hematological malignancy; persons receiving immunosuppressive therapy for other illnesses (e.g., rheumatoid arthritis); persons with HIV infection and a CD4 count <200; persons on dialysis; and women who are in the second or third trimester of pregnancy.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Of the large group of persons who are at increased risk of severe disease or death from influenza, these groups represent the population at highest risk and who are least likely to be protected by vaccination. Studies show that neuraminidase inhibitor therapy decreases complications and hospitalizations from influenza in high-risk persons and one unpublished study shows a significant decrease in mortality among patients who have undergone a hematopoietic stem cell transplant.

d) Population size

About 150,000 persons have had an HSCT or solid organ transplant. Assuming that the period of severe immunosuppression after a cancer diagnosis lasts for 1 year, the population targeted with non-skin, non-prostate cancers would equal the incidence of about 1.35 million persons. Based on a birth cohort of 4.1 million, a 28-week risk period during the second and third trimesters, and an 8-week pandemic outbreak in a community, there would be about 400,000 pregnant women included in this risk group. Further work is needed to estimate the size of other immunosuppressed groups.

e) Unresolved issues

Specific definition of included groups and population sizes.

4. Pandemic health responders, public safety workers, and key government decision-makers

a) Definition

Public health responders include those who manufacture vaccine and antiviral drugs; persons working at health departments who are not included as healthcare workers; and those who would be involved in implementing pandemic vaccination or other response components. Public safety workers include police, fire, and corrections personnel. Key government decision-makers include chief executives at federal, state, and local levels.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Preventing adverse health outcomes and social and economic impacts in a pandemic depend on the ability to implement an effective pandemic response. Early treatment of pandemic responders will minimize absenteeism and ensure that vaccination and other critical response activities can be maintained. Implementing early treatment for public health workers and vaccine manufacturers is feasible at workplace settings. Public safety workers prevent intentional and unintentional injuries and death, are critical to maintaining social functioning, and will contribute to a pandemic response, for example by ensuring order at vaccination clinics. A small number of decision-makers at federal, state, and local levels are needed to for an effective pandemic response.

d) Population size

An estimated 40,000 workers who produce pandemic vaccine and antiviral drugs in the U.S.; ~300,000 public health workers who would not be included in the HCW category; 3 million public safety workers; and a small number of government decision-makers.

e) Unresolved issues

Need to define the exact composition and size of this group.

5. Outpatients at increased risk of severe morbidity or mortality from influenza

a) Definition

For planning purposes, this group would include those currently designated as high-risk groups, except for those who have been categorized as being at highest-risk and included in a separate category. This increased-risk group includes persons 6-23 months and >65 years old, or who have underlying illnesses defined by the ACIP as associated with increased risk. Definition of this group may change based on the epidemiology of the pandemic.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Early treatment has been shown to significantly decrease lower respiratory infections and reduce the rate of hospitalization in elderly and high-risk populations. By extrapolation and based on the results of one small uncontrolled study, significant reductions of mortality can be expected as well. As these risk groups are familiar to the public given recommendations for annual vaccination, communication would be easy and acceptability high.

d) Population size

About 85.5 million persons are included in this group. Although all are at increased risk of annual influenza compared with the healthy under-65 year old population, there are different levels of increased risk for severe complications and death within this category. Further stratification may be possible based on several parameters including number of underlying conditions; recent hospitalization for a high-risk condition, pneumonia, or influenza; and age.

e) Unresolved issues

Stratifying this group into those at greater and lesser risk may be important if antiviral supplies are limited. Implementing treatment will be challenging given that it should be provided at the initial point of care to accrue the greatest benefit from early therapy.

6. Outbreak control

a) Definition

Use of antiviral drugs to support public health interventions in closed settings where an outbreak of pandemic influenza is occurring.

b) Strategy

Treatment of cases and post-exposure prophylaxis of contacts (once daily antiviral medication for 10 days).

c) Rationale

Influenza outbreaks in nursing homes are associated with substantial mortality and morbidity. Nursing home residents also are less likely to respond to vaccination. Post-exposure prophylaxis has been shown to be effective in stopping influenza outbreaks in closed settings.

d) Population size

The number of outbreaks that may occur during a pandemic is unclear. Measures should be implemented to prevent outbreaks including limiting visitors, vaccination of staff, furloughing non-critical staff, and screening and exclusion for illnesses consistent with influenza.

e) Unresolved issues

Should this policy also be implemented in prisons or other settings where explosive spread of illness may occur but the risk for severe complications is not high?

7. Healthcare workers in ER, ICU, EMS, and dialysis settings

a) Definition

Includes all staff in these settings who are required for effective functioning of these health care units.

b) Strategy

Prophylaxis

c) Rationale

Optimally effective functioning of these units is particularly critical to reducing the health impacts of a pandemic. Prophylaxis will minimize absenteeism in these critical settings.

d) Population size

Need to obtain population estimates.

e) Unresolved issues

Population sizes

8. Pandemic societal responders and healthcare workers who have no direct patient contact

a) Definition

This group includes persons who provide services that must be sustained at a

sufficient level during a pandemic to maintain public well-being, health, and safety. Included are workers at healthcare facilities who have no direct patient contact but are important for the operation of those facilities; utility (electricity, gas, water), waste management, mortuary, and some transport workers.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Maintaining certain key functions is important to preserve life and decrease societal disruption. Heat, clean water, waste disposal, and corpse management all contribute to public health. Ensuring functional transportation systems also protects health by making it possible for people to access medical care and by transporting food and other essential goods to where they are needed.

d) Population size

Within these broad categories, there are about 2 million workers at healthcare facilities who have no direct patient contact; 730,000 utility workers; 320,000 waste management workers; 62,000 in mortuary services; and 2.3 million in transportation. Not all occupations within these categories would be classified as pandemic societal responders. Estimates are that 35% of this population will develop illness and present within 48 hours of onset regardless of pandemic severity.

e) Unresolved issues

Need to stratify within these groups to identify who fills specific pandemic societal response functions and to assess whether those functions could still operate if a substantial proportion of the workforce became ill during a 6-8 week pandemic outbreak within a community. Implementation issues need to be addressed, especially with respect to how persons would be identified as falling within this priority group when presenting for treatment and where that treatment would be provided.

9. Other outpatients

a) Definition

Includes persons not in one of the earlier priority groups.

b) Strategy

Treatment within 48 hours of illness onset.

c) Rationale

Treatment reduces the risk of complications and mortality, reduces duration of illness and shortens time off work, and decreases viral shedding and transmission. If sufficient antiviral supplies are available, providing treatment to all who are ill achieves equity and will be most acceptable to the public.

d) Population size

There are an estimated 180 million persons who are not included in previously targeted groups.

e) Unresolved issues

Consider whether there are any strata that can be defined within this population.

C. Additional NVAC recommendations on antiviral drugs for pandemic influenza

In addition to recommendations for priority groups, NVAC unanimously adopted the following recommendations:

- Sufficient drugs should be stockpiled to address top priorities. NVAC recommends that the minimum stockpile size be about 40 million courses, allowing coverage of the top 7 priority groups.
- Oseltamivir should be the primary drug stockpiled, but some zanamivir also should be obtained as it is effective against some oseltamivir-resistant strains, may be preferred for treatment of pregnant women, and supporting two manufacturers enhances security against supply disruptions. Approximately 10% of the stockpile should be zanamivir if feasible and cost effective. No additional adamantanes should be stockpiled.
- Antiviral drugs can also be used as part of an international effort to contain an initial outbreak and prevent a pandemic. Use to slow disease spread early in a pandemic may be useful but requires large amounts of drug.
- Critical research should be conducted to support development and implementation of recommendations for pandemic influenza antiviral drug use, including:
  - Impact of treatment at hospital admission on outcome
  - Optimal treatment dose for H5N1 and other potential pandemic strains
  - Sensitivity and use of rapid diagnostic tests for H5N1 and other influenza strains with pandemic potential
  - Safety and pharmacokinetics of oseltamivir among infants <1 year old
  - Investigation of the impact of other drugs (new antiviral agents and other classes such as statins) on influenza
- Additional work with public and private sector groups should be done to further hone definitions of target groups and their estimated population sizes, and to provide further guidance on antiviral drug distribution and dispensing.